STATISTICAL ANALYSIS PLAN

NCT Number: NCT04056455

Study Title: A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects With Severe Renal Impairment and Normal Renal Function

Study Number: TAK-788-1007

SAP Version and Date:

Version 1.0: 18-Feb-2021

STATISTICAL ANALYSIS PLAN

Study Number: TAK-788-1007

Celerion Study Number: CA27460

Study Title: A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects with Severe Renal Impairment and Normal Renal Function

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Version	Approval Date	Primary Rationale for Revision
Original version	18-Feb-2021	Not Applicable

1.1 Approval Signatures

Electronic signature can be found on the last page of this document.

Study Title: A Phase 1 Pharmacokinetic Study of Oral Mobocertinib in Subjects with Severe Renal Impairment and Normal Renal Function

Approvals:

[redacted] PhD
[redacted] Statistical and Quantitative Science
Takeda Pharmaceuticals

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 ABBREVIATIONS

%Dose	percentage of dose eliminated
λ_z	terminal disposition phase rate constant
AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t
ANOVA	analysis of variance
AUC_∞	area under the total concentration versus time curve from time 0 extrapolated to infinity
$AUC_{\infty,u}$	area under the unbound concentration versus time curve from time 0 extrapolated to infinity
AUC_{last}	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration for total analyte
$AUC_{last,u}$	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration for unbound analyte
BLQ	below the lower limit of quantitation
BMI	body mass index
BP	blood pressure
CI	confidence interval
CL/F	apparent clearance after extravascular administration for total analyte
CL_R	renal clearance
CL_u/F	apparent clearance after extravascular administration for unbound analyte
C_{max}	maximum observed total plasma concentration
$C_{max,u}$	maximum observed unbound plasma concentration
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
Cum%Dose	cumulative percentage of dose eliminated
CumAe	cumulative amount eliminated
CV%	arithmetic percent coefficient of variation
DDFM	denominator degrees of freedom
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
fe_t	fraction of administered dose excreted in urine from time 0 to time t
Geom CV%	geometric percent coefficient of variation
Geom Mean	geometric mean
HR	heart rate
ICF	informed consent form
KR	Kenward-Roger
LSM	least-squares mean
Mean	arithmetic mean

MedDRA	Medical Dictionary for Regulatory Activities
MDRD	modification of diet in renal disease
n	number of observations
NCI	National Cancer Institute
PFT	pulmonary function test
PK	Pharmacokinetic
PO	per os (by mouth)
PT	preferred term (MedDRA)
RI	renal impairment
SAE	serious adverse event
SAP	statistical analysis plan
Scr,std	serum creatinine (mg/dL) measured with a standardized assay
SD	standard deviation
SEM	standard error of the mean
SI	International System of Units
SOC	system organ class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	Time of first occurrence of C_{max} and $C_{max,u}$
V_z	apparent volume of distribution during the terminal disposition phase after extravascular administration for total analyte
$V_{z,u}/F$	apparent volume of distribution during the terminal disposition phase after extravascular administration for unbound analyte
WHO	World Health Organization

4.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

4.1 Objectives

4.1.1 Primary Objective

To characterize the single-dose plasma and urine pharmacokinetics (PK) of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe renal impairment (RI) compared to matched-healthy subjects with normal renal function.

4.1.2 Secondary Objectives

1. *To evaluate plasma protein binding of mobocertinib, and its active metabolites (AP32960 and AP32914).*
2. *To assess the safety of mobocertinib following single oral dose in subjects with severe RI and the matched-healthy subjects with normal renal function.*

4.1.3 Exploratory Objective

To assess the overall fecal microbiome diversity, serum bacterial antibodies and/or other circulating biomarkers at the baseline.

Note: This exploratory objective will not be assessed by Celerion.

4.2 Endpoints

4.2.1 Primary Endpoints

The primary endpoints of the study are the following total and unbound PK parameters for mobocertinib and its active metabolites, AP32960 and AP32914 (bound and unbound parameters in parenthesis, respectively):

- *Maximum observed concentration (C_{max} and $C_{max,u}$).*
- *Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞} and $AUC_{\infty,u}$).*
- *Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last} and $AUC_{last,u}$).*
- *Combined molar unbound $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ of mobocertinib, AP32960, and AP32914.*
- *Time of first occurrence of C_{max} (t_{max}).*
- *Terminal disposition phase half-life ($t_{½z}$).*
- *Terminal disposition phase rate constant (λ_z).*

- *Apparent clearance after extravascular administration (CL/F and CL_u/F) for mobocertinib only.*
- *Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F and $V_{z,u}$/F) for mobocertinib only.*

The following urinary PK parameters will be analyzed for mobocertinib and its active metabolites, such as AP32960 and AP32914:

- *Amount of drug excreted in urine from time 0 to time t (Ae_t).*
- *Fraction of administered dose excreted in urine from time 0 to time t (fe_t).*
- *Renal clearance (CL_R).*

4.2.2 Secondary Endpoints

Pharmacokinetics

Plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914).

Safety

- *Incidence of treatment-emergent adverse events (TEAEs) assessments (including physical examination findings).*
- *Clinical laboratory testing.*
- *12-lead electrocardiogram (ECG).*
- *Vital signs.*

4.2.3 Exploratory Endpoints

Evaluation of baseline microbiome diversity in subjects with RI or subjects with normal renal function.

Note: This exploratory endpoint will not be determined by Celerion.

4.3 Estimand(s)

Not applicable.

5.0 STUDY DESIGN

This is an open-label, parallel-arm study of oral mobocertinib designed to assess the PK of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI compared to matched-healthy subjects with normal renal function.

Table 5:1 Study Arms and Planned Dose

Study Arms				
Arm	***Number of Subjects***	***Classification***	***eGRF(a) mL/min***	***Dose***
1	*12*	*Severe*	*15-29*	*80 mg*
2	*12*	*Matched-Healthy (b)*	*≥90*	*80 mg*

(a) Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation as defined as follows (for females multiply result by 0.742, if African American multiply result by 1.212):

$eGFR = (175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203})/1.73\ m^2$ (for subjects with standard BSA)

$eGFR = (175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203}) \times BSA\ value/1.73\ m^2$ (for subjects with non-standard BSA)

$S_{cr,\ std}$: serum creatinine (mg/dL) measured with a standardized assay.

BSA will be calculated using Dubois and Dubois formula (Dubois and Dubois, 1916)

(b) Healthy subjects with normal renal function will be recruited to match subjects in severe RI arm by age (mean ± 10 years), gender (± 2 subjects per gender), and body mass index (BMI, mean ±10%).

The study will consist of a 21-day screening period, a 10-day confinement period (Day −1 to Day 10), and a follow-up phone call 30 ± 2 days after dosing.

Subjects will receive a single oral dose of 80 mg mobocertinib capsule on Day 1.

Table 5:2 Study Design for Arms 1 and 2

Study Day	***S***	***-1***	***1***	***2***	***3***	***4***	***5***	***6***	***8***	***10***
Mobocertinib PO (80 mg)			*X*							
PK Blood Samples			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
PK Urine Samples			*X*	*X*	*X*	*X*	*X*	*X*		
Blood Sample for Bacterial Antibodies and Other Circulating Biomarkers	*X*									
Stool Sample for Microbiome Research	*X*									
Confinement in CRU		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*

CRU-clinical research unit; PK-pharmacokinetic; PO-per os (by mouth); S-screening.

Blood samples will be collected from Days 1 to 10 and urine PK samples will be collected from Day 1 to the morning of Day 6 at predetermined time points to characterize the plasma and urine PK and plasma protein binding of mobocertinib and its active metabolites (AP32960 and AP32914) in subjects with severe RI and in matched-healthy subjects with normal renal function.

Spirometry, as the pulmonary function test (PFT), may be performed in the event of a pulmonary adverse event (AE), if deemed clinically necessary by the Investigator or designee.

Subjects will be confined in the clinical research unit (CRU) from Day -1 until the morning of Day 10 after the 216-hour study assessments are complete. A subject may be required to remain at the CRU for longer periods, at the discretion of the Investigator. Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements.

A final safety follow up phone call will occur 30 ± 2 days after mobocertinib dosing to determine if any AEs have occurred since last study visit.

6.0 STATISTICAL HYPOTHESES AND DECISION RULES

6.1 Statistical Hypotheses

Not applicable.

6.2 Statistical Decision Rules

Not applicable.

6.3 Multiplicity Adjustment

Not applicable.

7.0 SAMPLE-SIZE DETERMINATION

The planned sample size of 12 subjects in each renal function arm is considered adequate to provide a precise estimation of the combined molar AUC_∞ of mobocertinib and its active metabolites AP32960, and AP32914 in subjects with severe RI compared to healthy subjects with normal renal function. The sample size calculation was based on the 95% confidence interval (CI) for the geometric mean of the combined molar AUC_∞ of mobocertinib and its active metabolites AP32960, and AP32914. The average interpatient coefficient of variation for mobocertinib, AP32960, and AP32914 apparent clearance was estimated to be [redacted] *With a sample size of 12 in each renal function arm, the 95% CI for the geometric mean of the combined molar AUC_∞ is expected to be 0.6 to 1.4 with at least 80% power according to the variance assumptions.*

8.0 ANALYSIS SETS

8.1 Safety Analysis Set

All subjects who received the dose of study drug will be included in the safety evaluations.

8.2 Pharmacokinetic Analysis Set

Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses. Any subject who experiences emesis within 8 hours post dosing with mobocertinib will be included in the PK analysis but excluded from the statistical analysis.

9.0 STATISTICAL ANALYSIS

9.1 General Considerations

All plasma PK analyses will be conducted using Phoenix® WinNonlin® Version 8.1 or higher. All urine PK analyses will be conducted using SAS® Version 9.4 or higher. All statistical analyses will be conducted using SAS® Version 9.4 or higher. All relevant data recorded in the electronic case report form (eCRF) will be listed by subject. All tables, figures, and listings (TFLs) shells and numbering list will be included and specified in the TFL Shells document.

Plasma and urine concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of plasma concentration plots, and the calculation of PK parameters, unless they are obvious outliers (e.g., BLQ value between measurable values (applicable for plasma concentrations only)), in which case they will be treated as missing.

For urine data, if a subject is unable to void in a given collection interval:

- urine sample weight will be set to 0,
- urine analyte concentration will be set to missing,
- amount eliminated (Ae_t) and percentage of dose eliminated (%Dose) will be set to 0,
- cumulative amount eliminated (CumAe) and cumulative percentage of dose eliminated (Cum%Dose) will be carried over from the previous interval.

A subject's plasma and/or urine PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical analyses if one or more of the following criteria are met:

- A predose (0 hr) plasma concentration is greater than 5% of that subject's maximum concentration value in that period
- If some urine is spilled for a given subject in a given collection interval, urine sample weight, urine analyte concentration, Ae, CumAe, %Dose, Cum%Dose, and CL_R will be presented but excluded from descriptive statistics

- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

The details on plasma and urine PK parameter calculations and TFLs will be outlined in the Clinical Pharmacology Analysis Plan (CPAP) and TFL Shell document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters
- PK parameters presented by renal function group, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by renal function group, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- Analysis of variance (ANOVA) results presented in in-text and end-of-text tables
- Arithmetic mean plasma concentration-time and urine Cum%Dose-time figures presented as in-text and end-of-text figures
- Individual plasma concentration-time and urine Cum%Dose-time figures.

All concentration and PK parameter data and their descriptive statistics (with the exception of the number of observations) will be presented to 3 significant digits. The number of observations (n) will be presented as an integer (no decimal places).

For demographic and safety data where appropriate, variables will be summarized descriptively. For the categorical variables, the counts and percentages of each possible value will be tabulated, where applicable. The denominator for the percent calculation will be based on the number of subjects dosed. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers.

9.1.1 Handling of Treatment Misallocations

Not applicable.

9.2 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

9.3 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized by renal function arm (ie, Severe RI, Normal Renal Function) and overall. Study completion status, including reason for discontinuation, will also be listed by subject.

9.4 Demographic and Other Baseline Characteristics

9.4.1 Demographics

Demographic and baseline characteristics will be summarized descriptively by renal function arm (ie, Severe RI, Normal Renal Function) and overall. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [recorded in the eCRF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI recorded at screening will be used in the baseline summaries. Demographics data will also be listed as recorded in the eCRF, including the date of informed consent.

9.4.2 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include any significant conditions or diseases that resolved at or before signing the informed consent form (ICF). Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug(s) will be classified as an adverse event. All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0. If appropriate, the medical history listing will include whether the event was medical or surgical, the body system or organ class involved, coded term, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

9.4.3 Baseline Characteristics

For assessment of renal function at screening, eGFR will be calculated based on MDRD formula for the renal classification category of either severe renal impairment or normal renal function and compared to the renal function assignment from historical values within a 6 month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (at least 72 hours apart). If the results of the two most recent assessments are not in agreement with regard to the subject's renal function category, the third assessment has to be performed at least 72 hours after the second assessment. Baseline renal function assessments will be listed by subject.

9.5 Medication History and Concomitant Medications

Medication history to be obtained includes any medication taken prior to clinic check-in. Concomitant medication includes any medication other than study drug taken at any time between Day 1 through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the WHO Drug Dictionary March 2020 B3 Global and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and end date, or whether it continued after study completion, and indication for use.

9.6 Efficacy Analysis

Not applicable.

9.7 Safety Analysis

For each renal function arm (ie, Severe RI, Normal Renal Function) safety and tolerability will be assessed through incidence, severity and type of adverse events. Safety will also be assessed through changes from baseline in subjects' vital signs, safety ECGs and clinical laboratory assessments; along with physical examinations. All safety data will be listed by, renal function arm (ie, Severe RI, Normal Renal Function), subject, and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

9.7.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity, relationship to study drug (related or not related) and action relative to the study drug as recorded in the eCRF. All AEs occurring during this study will be coded using the MedDRA® Dictionary Version 23.0. However, only TEAEs occurring after dosing will be summarized. A TEAE is defined as any AE newly occurring or worsening from the first dose until a follow-up phone call 30 days (±2 days) after the last dose of study drug. If a subject experiences an exacerbation or complication of a concurrent medical condition that should be recorded as an AE.

All AEs, including TEAEs, will be severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, with grading levels 1 to 5 which correspond to mild, moderate, severe or medically significant but not immediately life-threatening, life-threatening consequences, and fatal.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summaries will be presented by renal function arm (ie, Severe RI, Normal Renal Function). Summary tables will include number of subjects reporting the AE and as percent of safety analysis set by renal function group (ie, Severe RI, Normal Renal Function) and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >5% of all subjects in each renal function arm, excluding serious adverse events [SAEs]) will also be summarized. In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each renal function arm (ie, Severe HI, Normal Renal Function).

Additional TEAE summary tables will be presented by severity and relationship to study drug.

AEs with missing or unknown severity will be considered as severe (or Grade 3). AEs with missing or unknown relationship to study drug will be counted as related. AEs with missing date will be counted as treatment-emergent, unless the date is known to be prior to dosing. AEs with a start date on Day 1 but missing start time will be counted as treatment-emergent. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. For each relationship to study drug, if a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and SAEs will be discussed in the text of the CSR.

9.7.2 Adverse Events of Special Interest (if applicable)

Not applicable

9.7.3 Clinical Laboratory Assessments

Hematology, serum chemistry, coagulation, and urinalysis will be performed at screening, check-in (Day -1), Day 5, and Day 10 (or at early termination if applicable). Urine drug screening will be carried out at screening and check-in (Day-1) only. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by renal function arm (ie, Severe RI, Normal Renal Function) and assessment time points. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including rechecks (by replacement), taken prior to dosing (generally Day -1). All clinical laboratory listings and tables will be presented with the International System of Units (SI). Postdose unscheduled or recheck assessments, including early termination, will not be used in analysis.

For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be listed with the corresponding categorical references as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. All clinically significant laboratory tests, as indicated by the Investigator, and the corresponding values will be listed by subject in a table. All clinical laboratory data will be presented in by-subject data listings.

9.7.4 Vital Signs

Vital sign measurements consist of body temperature, respiratory rate, BP, and HR. Temperature and respiratory rate will be collected at screening only. BP and HR will be collected at screening, prior to dosing on Day 1, Day 1 hours 4 and 12, Day 2 (24 Hours), and Day 10 (or at early termination if applicable). Additional unscheduled vital signs may be recorded at other times if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for HR and BP results and change from baseline by renal function arm (ie, Severe RI, Normal Renal Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including rechecks (by replacement), taken prior to dosing. Postdose unscheduled or recheck assessments, including early termination, will not be used in analysis. Vital sign data will also be displayed in a data listing by subject.

9.7.5 Electrocardiograms

Single 12-lead ECGs will be collected at screening, prior to dosing on Day 1, Day 1 Hour 4, Day 2 (Hour 24), and Day 10 (or at early termination if applicable). Additional unscheduled ECGs may be recorded at other times if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by renal function arm (ie, Severe RI, Normal Renal Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including rechecks (by replacement), taken prior to dosing. Postdose unscheduled or recheck assessments, including early termination, will not be used in analysis. ECG data will also be displayed in a data listing by subject.

9.7.6 Physical Examination

Physical examination will be performed at screening, check-in, and at Day 10 (or early termination). If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), the check-in assessment will be conducted at the discretion of the Investigator. Symptom-driven physical exams may be performed at other times at the discretion of the Investigator. Physical

exam findings will be presented in the data listings by renal function arm (ie, Severe RI, Normal Renal Function) and subject.

9.7.7 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

9.7.8 Other Safety Analysis (if applicable)

Spirometry, as the pulmonary function test *(PFT), may be performed in the event of a pulmonary AE, if deemed clinically necessary by the Investigator or designee.*

9.7.9 Extent of Exposure and Compliance

The date, time, and treatment administered will be listed by subject.

9.8 Pharmacokinetic Analysis

Blood and urine samples for the assessment of plasma and urine mobocertinib, AP32960, and AP32914 concentrations, and blood samples for the assessment of plasma protein binding will be collected as outlined in Table 9:1 below:

Table 9:1 Collection of Blood Samples for Pharmacokinetic and Plasma Protein Binding Analyses and Urine Samples for Pharmacokinetic Analysis

Analyte	Matrix	Scheduled Time (Hours)*
Mobocertinib, AP32960, and AP32914	Plasma	Predose, and 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 168, and 216 hours postdose.
Protein Binding	Plasma	2, 4, and 24 hours postdose
Mobocertinib, AP32960, and AP32914	Urine	Predose, 0 - 12, 12 - 24, 24 - 36, 36 - 48, 48 - 72, 72 - 96, and 96 - 120 hours postdose.

*The actual dates and times of sample collections will be recorded on the source document in the case report form.

9.8.1 Plasma Pharmacokinetics

Plasma PK analysis will be described in the CPAP for this study.

The ln-transformed Combined Molar $C_{max,u}$, Combined Molar $AUC_{last,u}$, and Combined Molar $AUC_{\infty,u}$ will be compared between subjects with severe RI and subjects with normal renal function using an analysis of variance (ANOVA) model.

The ANOVA model will include renal function group (ie, Severe RI, Normal Renal Function) as a fixed effect and subject nested within group as a random effect. Each ANOVA analysis will calculate the least-squares means (LSMs), the difference between group LSMs, and the standard error associated with the difference. Residual, subject nested within arm, and inter-subject variance will be reported. Ratios of LSMs and 90% confidence intervals will be calculated using

the exponential function of the difference between group LSMs from the analysis on the ln-transformed Combined Molar $C_{max,u}$, Combined Molar $AUC_{last,u}$, and Combined Molar $AUC_{\infty,u}$. The above analysis will also be performed on the ln-transformed Combined Molar C_{max}, Combined Molar AUC_{last}, and Combined Molar AUC_{∞}.

The same analysis will be repeated for each analyte (mobocertinib, AP32960, and AP32914) separately and will be performed on both unbound ($C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$) and total (C_{max}, AUC_{last}, and AUC_{∞}) PK parameters.

The following SAS® code will be used to perform the analysis:

```
PROC MIXED DATA=XXX;
CLASS Arm Subject;
MODEL <ln_pkparam>=Arm/DDFM=KR;
RANDOM Subject(Arm);
ESTIMATE 'Severe Renal Impairment vs. Normal Renal Function' Arm 1 -1 / CL ALPHA=0.1
E;
LSMEANS Arm;
RUN;
```

9.8.2 Urine Pharmacokinetics

Urine PK analysis will be described in the CPAP for this study.

No inferential statistical analyses will be performed on PK parameter data in urine.

9.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

9.10 Preliminary Analyses

Plasma PK analysis will be completed as described in the CPAP and Section 9.8.1 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times will be used for the calculation of PK parameters (not actual sampling times); 3) tables and figures will be created using Phoenix® WinNonLin® Version 8.1 or higher.

9.11 Interim Analyses

Not applicable.

9.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

10.0 REFERENCES

Not applicable.

11.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The analyses described in this SAP do not differ from those specified in the protocol.

12.0 APPENDIX

12.1 Changes From the Previous Version of the SAP

Not applicable.

12.2 Data Handling Conventions

Not applicable.

12.3 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analyses provided in the CSR.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	18-Feb-2021 19:27 UTC